EXHIBIT O

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MARYLAND SOUTHERN DIVISION

Seymour Fein	*	
Plaintiff,	*	
v.	*	**Case No. 8:15-cv-03709-PWG**
ChiRhoClin, Inc.	*	
Defendant.	*	

REPORT AND OPINION OF DAVID LIN, Ph.D.

The undersigned was retained by ChiRhoClin, Inc. ("ChiRhoClin" or "Defendant") to review various documents, materials, and other information that concern a dispute between ChiRhoClin and Dr. Seymour Fein. The dispute primarily concerns a May 4, 2005 letter agreement (the "Letter Agreement") entered into between ChiRhoClin and Dr. Fein. The Letter Agreement is alleged to entitle Dr. Fein a royalty payment of 15% of ChiRhoClin's gross revenues from the sale of synthetic human secretin ("hsecretin") and synthetic porcine secretin ("psecretin"). The Letter Agreement provides, "[t]he obligation to pay this royalty will begin when the Company regains the right to sell psecretin."

I have been asked to provide my opinions regarding the United States Food and Drug Administration ("FDA") regulations, guidance and practices governing the requirements for qualification of a drug manufacturer. This report sets forth my opinions and the basis for those opinions.

I. SUMMARY OF CREDENTIALS AND EXPERIENCE

1. Since January 2005, I have been employed as a Senior Consultant at Biologics Consulting Group, Inc. ("BCG"), a team of consultants who provide national and international regulatory and product development advice on the development and commercial production of small molecular weight synthetic drug, biotechnological and biological products.

2. Before joining BCG, I held various positions with the FDA. From 1997-2001, I was a Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research ("CDER"). In 2001, I became the Team Leader in the same Division and served in that role until 2003, when I was promoted to the position of acting Deputy Division Director in the Division of New Drug Chemistry III, Office of New Drug Chemistry (currently referred to as Office of New Drug Quality Assessment). In 2004, I was promoted to the position of acting Division Director.

3. As a Chemistry Reviewer at CDER, I was responsible for the comprehensive review of Chemistry, Manufacturing and Controls ("CMC") data for drugs being investigated during Phase 1, 2, and 3 clinical studies. I was also responsible for the review of CMC data in Investigational New Drug Applications ("INDs"), New Drug Applications ("NDAs"), and NDA post-approval Supplements. This included providing scientific and regulatory guidance during development of small molecular weight drugs and biotechnological/biological drugs across a wide variety of dosage forms.

4. As the acting Deputy Division Director and acting Division Director of the Office of New Drug Chemistry, I directly managed and supervised chemists with review responsibilities in the following six medical-reviewing divisions: (1) anti-inflammatory/analgesic/

ophthalmologic, (2) dermatologic/dental, (3) anti-viral, (4) anti-infective, (5) special pathogen/immunologic, and (6) over-the-counter drugs.

5. I have reviewed CMC data submitted with respect to over 100 INDs and NDAs (original and supplemental) as a chemistry reviewer, contributed to decisions regarding the approval of drugs, made presentations before scientific and regulatory conferences and participated in a variety of special FDA projects and committees, including serving as the co-Chair of the CMC Good Review Practices Committee.

6. As both a chemistry reviewer and acting Division Director I became experienced with FDA's expectations and requirements for approval of the CMC section of NDAs.

7. As Team Leader, acting Deputy Division Director and acting Division Director in the Office of New Drug Chemistry, I was actively involved in directing the content of FDA guidances that pertained to CMC topics. As acting Deputy Division Director and Division Director, I was directly involved in discussions regarding the content of the 2003 FDA draft guidance on Drug Product-Chemistry, Manufacturing, and Controls Information, with the committee responsible for writing this guidance. I had signatory authority for this draft guidance prior to public issuance by FDA.

8. I consider myself an expert in the fields of FDA practice and procedure as applicable to the review of INDs, NDAs and abbreviated new drug applications ("ANDAs").

9. Before joining FDA I was a staff scientist at General Electric Company's Biological Sciences Laboratory from 1989 to 1994, and a research assistant in the Department of Chemistry/Biochemistry at the University of Maryland from 1984-1989.

10. I received my B.A. in Biochemistry from the University of Pennsylvania in 1984, my Ph.D. in Organic Chemistry from the University of Maryland in 1989 and my M.B.A. from

the University of Maryland's RH Smith School of Business in 2002. Attached hereto as Appendix A is my curriculum vitae, including a list of my publications for the past ten years.

11. The following opinions and conclusions are based upon my education, training, experience, knowledge of the FDA, and my review of the documents and materials referenced herein and listed in Appendix B. I have provided expert testimony by trial or deposition in two cases in the past four years, which are listed in Appendix C. My hourly fee for work in this case is $500 per hour. All opinions provided herein are given to a reasonable degree of professional certainty within my field of expertise, unless otherwise specifically indicated.

II. SUMMARY OF OPINIONS

12. I agree with the Defendant's assertion, set forth in their Answer to Complaint and Counterclaims (the "Answer") that "would require CRC to embark on a multiyear FDA approval process requiring several regulatory steps" to "obtain the right to sell psecretin". Even with an approved NDA for psecretin, if the product had not been commercially manufactured it is reasonable to expect that it will require a period of time in order to be able to produce the product that meets the quality specifications for the product and also to demonstrate manufacturing consistency. The ability to start manufacturing for commercial distribution in a shorter time period assumes that manufacturing will be performed at the manufacturers specified in the NDA, so as to leverage their previous manufacturing experience. Otherwise, the introduction of new manufacturers for the product will require a longer time period to develop the manufacturing experience to produce commercial product that can meet the quality specifications specified in the NDA.

13. I further agree with the Defendant's assertion, set forth in the Answer, that requires "obtaining FDA approval for the re-labeling of its psecretin product because Repligen owned the trademark to SecreFlo®". The change in the proprietary name requires FDA approval

so that FDA can evaluate whether the name is similar to another proprietary name and could cause confusion to healthcare providers.[1, 2]

III. MATERIALS CONSIDERED

14. In support of my opinions, I have considered and relied on materials set forth in Appendix B, my knowledge and understanding of applicable FDA regulations, guidances, and practices, and my knowledge and experience with drug products over the course of my education and career.

IV. OVERVIEW OF DRUG REGULATIONS AND FDA CONSIDERATION OF EXISTING MANUFACTURING FACILITY QUALIFICATION FOR COMMERCIAL DISTRIBUTION

15. FDA is a federal agency responsible for, among other duties, ensuring that a drug marketed in the United States is safe and effective for use as prescribed in the labeling of the drug, and can be adequately manufactured, processed and packaged to preserve the drug's identity, strength, quality and purity.[3] There are additional rules, regulations and guidances that further delineate the requirements necessary to satisfy these statutory requirements.

16. Prescription drug products are closely scrutinized and regulated by FDA. Based on my more than 21 years of pharmaceutical regulatory experience, I am intimately familiar with the regulations, guidances, and practices governing prescription drug products.

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[1] Federal Food, Drug, and Cosmetic Act, § 502(a) (21 U.S.C. § 352(a)).

[2] Contents of a Complete Submission for the Evaluation of Proprietary Names: Guidance for Industry, Revision 1, April 2016.

[3] 21 U.S.C. § 355(d).

17. An original NDA requires comprehensive technical information concerning the drug, including "the drug[4] manufacturer(s)", "the manufacturing process and process controls for the drug", and "the specifications for the drug," among other things.[5, 6]

18. An NDA requires submission of the full reports of the investigations used to show that the drug is safe for use and is effective in use, the manufacturing facility of the drug, the methods used in and the facilities and controls used for the manufacturing, processing and packing of the drug, and the labeling for the drug.[7]

19. In order to determine whether a new drug product is safe and effective and can be brought to market, FDA requires pharmaceutical companies to conduct various scientific studies in addition to preclinical animal studies and clinical trials in humans. All drugs possess critical quality attributes that are necessary to ensure the safe and efficacious use of the drug product by patients. These quality attributes are assessed during the scientific studies through the use of drug manufactured with specified characteristics.

20. FDA evaluates not only the reports of the clinical investigations, but also the nonclinical pharmacology and toxicology studies conducted in animals, human pharmacokinetic and bioavailability studies, and CMC information.[8] It is this complete package of information and data that allows FDA to determine the safety and effectiveness of the drug, and the ability of the manufacturer to produce a consistent and quality drug.

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[4] Unless otherwise specified, the term "drug" refers to both the drug substance and drug product.

[5] 21 C.F.R. § 314.50(d)(1)(i).

[6] 21 C.F.R. § 314.50(d)(1)(ii)(a).

[7] 21 U.S.C. § 355(b)(1).

[8] 21 C.F.R. § 314.50.

21. The statutory provisions and regulations do not provide specific details on the information FDA requires in an NDA with respect to the manufacturing process and process controls used to manufacture the drug. However, FDA has issued guidance on the information and data recommended for inclusion in the NDA for a synthetic peptide drug substance[9], such as psecretin, and a drug product[10] for injection. This information includes the manufacturer and site of manufacturing, a detailed description of the manufacturing process and process controls, the specifications, and stability of the drug substance and drug product.

22. The Defendant currently has a FDA approved NDA which permits for the commercial distribution of the psecretin product. The manufacturing of psecretin product is not conducted by the Defendant but outsourced to contract manufacturers. This includes the manufacturing of the synthetic psecretin drug substance and the formulated psecretin as the drug product.

23. It is my understanding that the contract manufacturers have not manufactured product for commercial distribution for 8-9 years. For the Defendant to commence commercial distribution of the drug product, the manufacturing of the drug will have to be initiated at the contract manufacturers. As specified in guidance[10, 11], the approved NDA includes a detailed description of the manufacturing process and process controls for the drug substance and drug product. Therefore, for the contract manufacturers to initiate manufacturing, the manufacturing process and process controls for the drug substance and drug product must be the same as described in the approved NDA. The NDA also includes conditions such as defined in-process

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[9] FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1994 (withdrawn June 1, 2006).

[10] FDA Guidance for Industry: Drug Product - Chemistry, Manufacturing, and Controls Information, draft, January 2003 (withdrawn June 1, 2006).

tests and criteria for process intermediates in the manufacturing process, and quality specifications that the drug must meet. These in-process and quality specifications need to be met in order for the manufactured drug to be commercially distributed.

24. If during the initiation of the contract manufacturing the detailed manufacturing process and process control requirements remain the same as in the approved NDA, there are no requirements to report the manufacturing of the drug product to the FDA. However, the contract manufacturers are required under the current good manufacturing practice ("cGMP") regulations to demonstrate that they are capable of consistently manufacturing product that meets specifications prior to commercial distribution[11]. The contract manufacturers need to, at minimum, demonstrate that manufacturing process for the drug substance and drug product is validated. Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. § 351(a)(2)(B)), which states the following:

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

25. From a cGMP perspective if product has not been manufactured for the number of years that psecretin had not been manufactured (i.e., 8-9 years) revalidation of the existing

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[11] 21 C.F.R. § 211.100(a) and § 211.110(a).

process will be required. The current regulatory expectations for process validation are provided in the FDA guidance on process validation[12].

26. Demonstrating that the manufacturing process for the drug has been validated is more than just producing a fixed number of drug substance and drug product batches and showing that these batches meet the quality specifications. Assuming that the contract manufacturers had previously established the process design based on their experience with the manufacturing of the drug during clinical development and initial commercial manufacturing, then process performance qualification is needed.[13] The FDA guidance does not specify the number of batches that are required to be manufactured in order to determine that process validation has been accomplished sufficient for commercial distribution. This determination is left to the manufacturer and is based on the manufacturer's overall level of product and process understanding and demonstrable control. This includes the cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches).

27. Since the contract manufacturers have not manufactured the product for a number of years FDA is likely to inspect the manufacturing facility to determine whether the facility is in cGMP compliance. The inspection will be conducted by FDA inspectors in order to evaluate compliance to current standards and not necessarily to the standards in place in 2002. Depending on the manufacturing activities of the contract manufacturers for other FDA regulated drugs, the facility cGMP status could be out of compliance and require remediation in order to be compliant and to allow for the manufacture of commercial product. FDA will be particularly

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[12] FDA Guidance for Industry: Process Validation: General Principles and Practices, Revision 1, January 2011.

concerned with the cGMP compliance status of a manufacturer that previously had regulatory problems at that facility.

28. For these reasons, it is my opinion, based on FDA regulations and guidance, that prior to the commercial distribution of the approved psecretin drug product, qualification of the contract manufacturers specified in the approved NDA is required. In addition, due to the qualification of the manufacturers, immediate commercial distribution of the product under the approved NDA is not feasible.

V. FDA CONSIDERATION OF NEW MANUFACTURING FACILITY QUALIFICATION FOR COMMERCIAL DISTRIBUTION

29. The previous section provides the requirements for commercial manufacturing of the product using the contract manufacturers specified in the approved NDA. If these contract manufacturers no longer have the capability (i.e., lack of appropriate equipment, lack of appropriate personnel, lack of appropriate expertise, lack of cGMP compliance, etc.) to produce the product, the Defendant will have to seek other contract manufacturers with the capability to produce the product under cGMPs.

30. The regulatory requirements to replace the contract manufacturers in the approved NDA will require FDA approval as specified in the regulations for "supplements and other changes to an approved application"[13]. The type of submission is further delineated at 21 C.F.R. § 314.70(b). For "Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes)" a supplement must be submitted for any change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to

[13] 21 C.F.R. § 314.70(a).

the safety or effectiveness of the drug product[14] (also referred to as "Prior Approval Supplement"). These include changes in the drug substance, drug product, production process, quality controls, equipment, or facilities. These major changes require FDA approval of the supplement prior to distribution of the product made with the changes.[15] Examples of the major changes are provided in the regulations[16] and FDA guidance[17]. Based on regulation and guidance a new manufacturer for a sterile drug product is considered a major change and will require prior approval from FDA before product can be distributed using the change. FDA requirement to review and act on a prior approval supplement is 4 months[18]. This does not mean that FDA has to approve the supplement by 4 months but that they need to finish review and take an action on the supplement. If the supplement does not include adequate information and data to support the changes specified, which also includes a satisfactory cGMP inspection at the manufacturing facility, FDA will not approve the supplement. If the new manufacturer is not approved, then the product produced by the manufacturer cannot be commercially distributed.

31. As required for an original NDA, details of the manufacturer, manufacturing process, process controls, specifications and stability of the product are needed in the supplement. Even if the manufacturing process, process controls and specifications at the new manufacturer remain the same as in the approved NDA, there is a requirement to generate stability of the drug substance and drug product to demonstrate that the change to a new

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[14] 21 C.F.R. § 314.70(b)(1).

[15] 21 C.F.R. § 314.70(b)(3).

[16] 21 C.F.R. § 314.70(b)(2).

[17] Guidance for Industry: Changes to an Approved NDA or ANDA, Revision 1, April 2004.

[18] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017.

manufacturer does not have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. The amount of stability data for the drug substance and an injectable drug product is not specified in regulation or FDA guidance. However, there are FDA guidances for other dosage forms such as tablet[19, 20] and semi-solid[21] products that recommend the amount of stability data needed for inclusion in a supplement. In these guidances, FDA's expectation for the amount of drug product stability data is 3 months for 3 drug product batches.

32. A new manufacturer will be required to develop the manufacturing process for the product. Even with the availability of the manufacturing process and process control information in the approved NDA, the new manufacturer will need to qualify and validate the manufacturing process (per cGMP regulations[22, 23] and FDA guidance[24]. In addition, the new manufacturer is required to demonstrate satisfactory cGMP compliance during a FDA inspection. The duration of time that is required to satisfy the validation and cGMP compliance requirement can vary from months to years. Much of this will depend on the manufacturer's experience in the manufacture of this type of drug substance and sterile drug product dosage form. All of the

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[19] Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation, November 1995.

[20] Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997.

[21] Guidance for Industry: Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, May 1997.

[22] 21 C.F.R. § 211.100(a).

[23] 21 C.F.R. § 211.110(a).

[24] FDA Guidance for Industry: Process Validation: General Principles and Practices, Revision 1, January 2011.

facility compliance and manufacturing process validation efforts are required prior to the submission of a prior approval supplement.

33. On the basis of 21 C.F.R. § 314.70, there are two other types of supplements. One is for "Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes)"[25]. These are changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The other type is for changes requiring a supplement submission prior to distribution of the drug product made using the change (moderate changes).[26, 27] The types of changes that can be submitted in these "changes being effected" supplements are delineated in regulation and FDA guidance, but do not pertain to changes that may affect drug substance or drug product sterility assurance.[28, 29]

34. A final submission type for reporting changes to FDA is the NDA Annual Report.[30] "Changes to be described in an annual report (minor changes)" are for changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.[31] These changes only have to be reported to FDA but do not require approval.

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[25] 21 C.F.R. § 314.70(c).

[26] 21 C.F.R. § 314.70(c)(3).

[27] 21 C.F.R. § 314.70(c)(6).

[28] 21 C.F.R. § 314.70(b)(2)(iii).

[29] Guidance for Industry: Changes to an Approved NDA or ANDA, Revision 1, April 2004.

[30] 21 C.F.R. § 314.70(b)(2)(iii).

[31] 21 C.F.R. § 314.70(d).

However, these changes do not pertain to the addition of a new manufacturer or for the manufacture of a sterile drug product.

35. The new manufacturers will need to either develop the quality control test methods or follow the current test methods specified in the approved NDA. In either case, the manufacturer is required to validate the test methods.[32]

36. For these reasons, it is my opinion, based on FDA regulations and guidance, that prior to the commercial distribution of the approved psecretin drug product, addition of new manufacturers for the drug substance and drug product will require the execution of multiple activities such as manufacturing process validation, test method validation, stability data generation, cGMP compliance establishment and approval by FDA. These activities will preclude the immediate commercial distribution of the product under the approved NDA and will require a time period of months to years prior to the ability for commercial distribution.

VI. FDA REQUIREMENTS for LABELING CHANGES PRIOR to COMMERCIAL DISTRIBUTION

37. Prior to commercial distribution of the approved psecretin drug product, Repligen's trademark name, SecreFlo®, will be changed to a proprietary name that the Defendant proposes to FDA. This change in proprietary name requires submission of a prior approval supplement[33, 34] and therefore, requires FDA approval before revision of approved SecreFlo® name on the product labeling. The review and action timeline for a labeling prior approval supplement is the same as for a CMC prior approval supplement.

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[32] 21 C.F.R. § 314.70(d).

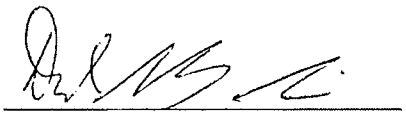
[33] 21 C.F.R. § 314.70(b)(2)(v)(A).

[34] 21 C.F.R. § 201.57(a)(2).

38. FDA's review and approval of a proprietary name is performed so that the name does not cause or contribute to medication errors, or otherwise contribute to the misbranding of the drug.[35] FDA considers a proposed proprietary name to be misleading if it may be confused with the proprietary name or the established name of a different drug or ingredient because of similar spelling or pronunciation.[36]

39. The opinions and conclusions expressed herein are based upon my education, training, experience, knowledge of the FDA, and my review of documents and materials referenced above. All opinions provided are given to a reasonable degree of professional certainty within my field of expertise, unless otherwise specifically indicated.

40. Because discovery is incomplete and continues in this matter, my opinions may be supplemented or amended as additional information, facts, or materials are made available through the discovery process.



David Lin, Ph.D.

Dated: May 27, 2016

[35] Guidance for Industry: Best Practices in Developing Proprietary Names for Drugs, draft, May 2014.

[36] 21 C.F.R. § 201.10(c)(5).